PATENT
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IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of:

BARTHOLEYNS et al.

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Application No. 10/622,727

Group 1642

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Examiner: Misook Yu

COMBINED PREPARATION FOR THE TREATMENT OF NEOPLASIC DISEASES OR OF INFECTIOUS DISEASES

DECLARATION UNDER RULE 132

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jean-Marie DUPUY, am Vice President of Medical Affairs of the current assignee, I.D.M. Immuno-Designed Molecules of Paris, France and hereby declare as follows:

I am familiar with the Examiner's position that the claimed method of treating a patient suffering from a neoplastic or infectious disease, comprising administering an effective amount of monocyte derived cells and an effective amount of chemotherapy drugs would have been obvious under 35 USC 103(a)because Bartoleyns et al. (Immunobiology 1996) disclose a method of treating cancer using monocyte derived cells and that stimulation against a tumor might only be successful when the tumor has been reduced to manageable by prior chemotherapy. We

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do not believe the publication teaches the claimed invention. Furthermore, the Official Action fails to appreciate the unexpected effects of administering an effective amount of both monocyte derived cells and chemotherapy drugs.

The following clinical study was conducted under my direction and demonstrates unexpected and even synergistic effects.

TEST DATA

An adoptive immunotherapy with activated macrophages (MAK) aimed with anti-HER2/neu x anti-FeγRI bispecific antibodies (e.g. MDX-H120) was sequentially combined with chemotherapy for the treatment of ovarian carcinoma.

The objective of this multicenter phase II pilot study was to evaluate the safety and the effect of the treatment on macroscopic or microscopic residual disease in patients with histologically proven ovarian epithelial cancer (stage III or IV).

Seventeen patients were evaluated for safety and efficacy out of a total of 17 patients included and treated, 14 were eligible.

Treatment:

The MAK cell preparations, nominally 10^9 cells, are mixed with 1.0 mg of MDX-H210 and administered intraperitoneally

The addition of MDX-H210 was initially dependent on the over expression status of HER-2/neu at the surface of tumour cells. The protocol was subsequently amended to treat all patients with the mixture of MAK cells + MDX-H210, regardless of their HER-2/neu status. After inclusion, an intraperitoneal injection device is surgically implanted. Each patient has a total of 6 aphereses (during a 4-week period) in order to prepare 6 doses of MAK + MDX-H210. Each dose is injected intraperitoneally via the implanted device 7 days following apheresis. The protocol treatment and observation scheme is summarized in Table L

Table I. Summary of treatment and evaluation schedule

At 2nd look laparotomy before day 1, evaluation of the size of the residual disease if macroscopic lesion and/or biopsies										
Day	1	4	8	11	15	22	25	29	32	36
Apheresis	X	X	X			X	X	X		
Infusion			X	X	X			X	X	X
At 3rd look lapartomy at month 3, evaluation of the size of the residual disease if macroscopic lesion and/or biopsies										

Special Safety Considerations about Apheresis Procedure:

Apheresis is a routine procedure for the selective collection of blood cells. In the three clinical studies using the MAK cell processor for a total of 310 apheresis procedures, no adverse or serious adverse events relating to the apheresis procedure have been reported.

To anticipate the likelihood of such events, each patient undergoes a pre-apheresis visit to establish whether the patient presents any contraindication to apheresis and is suitable for the procedure according to the MAK cell processor operating manual and local SOPs. This assessment is specified in the inclusion criteria of the proposed clinical study.

Tumour Response Evaluation:

After chemotherapy, a second look was performed. Patients were included in the study if macroscopic examination revealed a residual tumour of less than 1 cm and/or if the histological examination was positive. These residual tumors were therefore resistant to chemotherapy.

The evaluation of MAK treatment was carried out 3 months after the start of the treatment at the time of a third look performed during laparoscopy/laparotomy and biopsy analysis.

RESULTS

Safety of the immunotherapeutic/chemotherapeutic treatment:

A total of 100 MAK cell preparations were administered intraperitoneally to 17 patients. No serious adverse events related to the treatment were reported (one patient had a pulmonary embolism SAE five weeks after the last administration, unrelated to treatment). Only minor adverse events were observed.

Ten patients (59%) had at least one adverse event. A total of 23 adverse events were observed, grouped as follows:

- Body as a whole, general disorders in three patients (17%, chills, fever, lumbar pain, edema of the extremities).
- Gastro-intestinal system disorders in six patients (35%, abdominal pain, cramp, nausea, vomiting).
- Platelet, bleeding and clotting disorder in one patient (6%, pulmonary embolism) declared as a SAE.
- Central and peripheral nervous disorders in two patients (12%, neuropathy, distal paraesthesia).
- Psychiatric disorder in one patient (6%, hypochondriasis).

Nine patients (53%) had adverse events which were thought to be related to treatment. Seventeen out of the 23 adverse events were recorded as related to treatment, of which 13 had a possible relationship and four adverse events were definitely related to the treatment.

The main, adverse event related to treatment was in gastrointestinal disorders with five patients suffering from abdominal pain. This was thought to be due to the volume, temperature and/or speed of the intraperitoneal infusion for the

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production of an ascites in the peritoneum. Other related events included chills, fever, edema of the extremities, cramp, nausea, vomiting and hypochondriasis.

Biological safety evaluations were unremarkable except for platelet counts which fell after apheresis but recovered to normal levels within one week after the third apheresis on day 8. Values for RBC, haemoglobin, haematocrit, leukocytes, neutrophils and monocytes did not vary significantly between aphereses. This reflects the ability of the heamopoietic to respond to short term depletion of the white cell population. It should be remembered that these patients were neither immunologically nor haematologically compromised since they had completed cytotoxic chemotherapy at least four weeks earlier.

Efficacy of the immunotherapeutic/chemotherapeutic treatment:

Fourteen patients were eligible for efficacy analysis; all entered the study after first line chemotherapy. Eight out of nine who were HER-2/neu positive received MAK cells + MDX-H210. All five patients who tested HER-2/neu negative received MAK cells + MDX-H210.

All evaluated patients had residual cancer at 2nd look laparoscopy with macroscopic (7/14) at microscopic (7/14) lesions. Third look was performed in 11 out of 14 patients. Macroscopic lesions were observed in four cases (no change (NC) in two and additional tumours in two). In seven patients without

evidence of macroscopic residual tumour, multiple biopsies revealed microscopic signs of cancer in 2/7 and were negative on 5/7 (complete response, CR). Out of the five CR patients, four had no macroscopic lesions at 2nd look, but one patient presented at 2nd look with a positive nodule of 10 mm diameter and two or three granulous positive lesions which were surgically removed.

Three of five complete responses occurred in patients treated with MAK cells ± MDX-H210 (all three were HER-2/neu positive) and two in patients treated with MAK cells only: one was HER-2/neu negative and -the other was HER-2/neu positive.

Patients relapsing after first chemotherapy (Dr. Louvet's letter):

The patient MESM was re-treated with topotecan 6 months after the end of the treatment. She was partially responsiveness.

The patient ROBC exhibited a tumor progression 11 months after the start of the treatment. Then, she was treated with taxol and answered partially to these treatments.

The patient NABR relapsed 15 months after the start of the treatment. The chemotherapeutic treatment with Taxol-carboplatine induced a normalization of CA 125.

The patient TYMN relapsed 14 months after the start of the treatment. She was partially responsiveness to a cisplatine-epirubucune chemotherapy.

Tmn

Attached to this declaration is an identification of the patient's identification codes (MESM, ROBC, NABR, TYMN).

CONCLUSION

This phase II pilot study demonstrates the safety and efficacy of combined treatment (immunotherapy + chemotherapy) in patients with histologically proven ovarian epithelial cancer despite the deleterious effects of chemotherapy on cells. Patients were relapsing and in progression after chemotherapy and included in the MAK immunotherapy trial. After this treatment, the tumor progressed again in four patients, and these patients were treated again by chemotherapy, which was effective to induce a partial clinical response.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Jean-Marie Dupuy

Date 03 - 08 - 07

SUIVI DE l'ETUDE MACROPHAGES ACTIVES

- Patiente N°2 : MESM, inclusion au protocole le 5 décembre 1997. Traitement terminé le 19 janvier 1998. Reprise d'une chimiothérapie le 22 juillet 1998 : Topotécan : réponse partielle.

- Patiente N°8 : ROBC, inclusion au protocole le 21 octobre 1998. Progression le 15 septembre 1999. Reprise d'une chimiothérapie par Taxol : réponse partielle.

- Patiente N°11 : NABR, inclusion au protocole le 4 décembre 1998. Rechute le 16 mars 2000. Reprise d'une chimiothérapie par Taxol-Carboplatine : normalisation du CA 125 (maladie non mesurable pour la réponse).

- Patiente N°13 : TYMN , inclusion au protocole le 22 février 1999. Rechute le 15 avril 2000. Reprise d'une chimiothérapie par Cisplatine-Epirubucine : réponse partielle.

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STUDY ON ACTIVATED MACROPHAGES AND CHEMOTHERAPY

Patient n°2: MESM: inclusion to the protocol on December 5, 1997. Treatment which is ended on January 19, 1998. Renewal of chemotherapy on July 22, 1998 : Topotecan: partial clinical answer (*reduction of tumor size not complete, but higher than 50%*).

Patient n°9: ROBC: inclusion to the protocol on October 21, 1998. Progression on September 15, 1999. Renewal of a chemotherapy by Taxol: partial clinical answer;

Patient n°11: NABR: inclusion to the protocol on December 4, 1998. Relapse in March 15, 2000. Renewal of chemotherapy by Texol-Carboplatine: the tumor marker CA125 was normalized (disease which cannot be measured for the answer) (*tumor too small to be measured*)..

Patient n°13:TYMN: inclusion to the protocol on February 22, 1999. Relapse on April 15, 2000. Renewal of the chemotherapy by Cisplatine-Epirubucune : partial clinical answer.